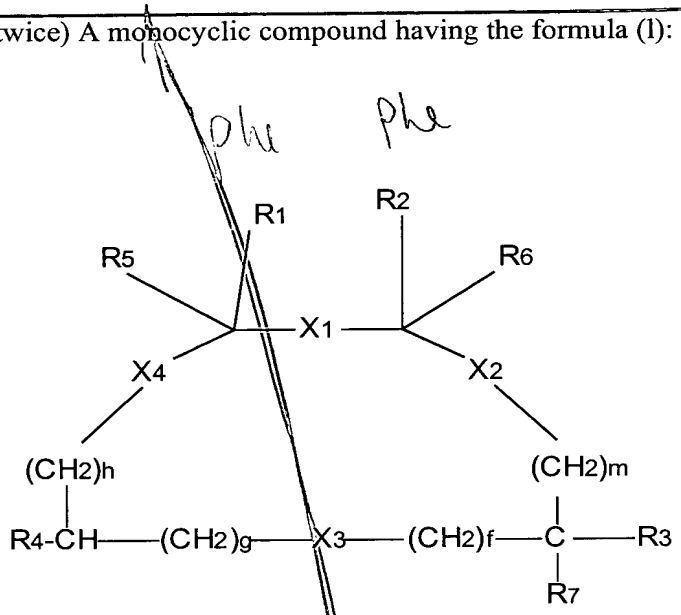
IN THE CLAIMS:

Kindly amend the Claims as follows:

1. (Amended twice) A monocyclic compound having the formula (I):



in which:

X_1, X_2, X_3, X_4, which may be the same or different from one another, is selected from the group consisting of -CONR-, -NRCO-, -OCO-, -COO-, $-CH_2NR-$ and $-NR-CH_2-$, where R is H or a C_{1-3} alkyl or benzyl;

f, g, h, m, which may be the same or different from one another, may be 0 or 1;

R_1 and R_2 which may be the same or different from one another, represent the side chain of a natural amino acid selected from the group consisting of tryptophan, phenylalanine, tyrosine and histidine, or the side chain of a non-natural amino acid selected from the group consisting of:

tryptophan and phenylalanine, either mono- or di-substituted with residues

selected from the group consisting of C_{1-3} alkyl or halo-alkyl, C_{1-3} alkoxyl or amino-alkoxyl, halogen, OH, NH_2 and $NR_{13}R_{14}$, where R_{13} and R_{14}, which may be the same or different from one another, represent a hydrogen or C_{1-3} alkyl group;

R_3 is selected from the group consisting of:

– linear or branched alkyl having the formula C_nH_{2n+1} with n = 1-5 (selected from the group consisting of methyl, ethyl, propyl, isopropyl, n-butyl and t-butyl) cycloalkyl or alkylcycloalkyl of formula C_nH_{2n-1} with n = 5-9 (selected from the group consisting of: cyclopentyl, cyclohexyl and methylcyclohexyl)

$-(CH_2)_r-Ar_1$, where r = 1 or 2 and where Ar_1 is an aromatic group selected from the group consisting of: α-naphthyl, β-naphthyl, phenyl, indole, said Ar_1 group being possibly substituted with a maximum of two residues selected from the group consisting of: C_{1-3} alkyl, CF_3, C_{1-3} alkoxyl, Cl, F, OH and NH_2;

R_4 represents an L-Q group where:

L is a chemical bond or CH_2, and

Q is selected from the group consisting of:

– OH, NH_2, NR_9R_{10}, OR_{11}, and where R_9 and R_{10}, which may be the same or different from one another, represent a hydrogen or C_{1-3} alkyl group, C_{1-3}hydroxy alkyl, C_{1-3}dihydroxyaklyl, C_{1-3}alkyl-$CONHR_{12}$ (wherein R_{12} is a monoglycosidic group derived from D or L pentoses or hexoses (selected from the group consisting of ribose, arabinose, glucose, galactose, fructose, glucosamine, galactosamine, N-acetylglucosamine and N-acetylgalactosamine, C_{1-3}alkyltetrazole, C_{1-3}alkyl-COOH or wherein R_9R_{10} are joined together to form with the N atom a morpholine or a piperidine ring and where R_{11} is a C_{1-3} alkyl chain, or a C_{2-4} amino-alkyl chain; $NHCOR_8$ wherein R_8 is a cyclohexane containing from 2 to 4 OH groups, C_{1-6} alkyl chain containing a polar group (chosen in the group consisting of NH_2, COOH, $CONHR_{12}$, (wherein R_{12} is as hereabove defined) or ([1,4']bipiperidine)

– COOH, $COOR_{17}$ or $CONHR_{12}$, wherein R_{12} is as hereabove defined and R_{17} is as R_{12} or a group 4-nitrobenzyl.

– R_5, R_6, R_7 are H_2

in which the carbon atom that carries the substituents R_3 and R_7 has configuration R.

3. (Amended three times) A compound according to Claim 2 selected from:

(a) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH($CH_2C_6H_5$)-CH_2-NH]}

(b) Cyclo{-Suc-Trp-Phe-[(S)-NH-CH($CH_2C_6H_5$)-CH_2-NH]}

(c) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH($CH_2C_6H_{11}$)-CH_2-NH]}

(d) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH($CH_2C_6H_4$(4-OCH_3))-CH_2-NH]}

(e) Cyclo{-Suc-Trp(5F)-Phe-[(R)- NH-CH($CH_2C_6H_5$)-CH_2-NH]}

(f) Cyclo{-Suc-Trp(Me)-Phe-[(R)- NH-CH($CH_2C_6H_5$)-CH_2-NH]}

(g) Cyclo{-Suc-Phe(3,4-Cl)-Phe-[(R)- NH-CH($CH_2C_6H_5$)-CH_2-NH]}

(h) Cyclo{-Suc-Trp-Phe(3,4-Cl)- [(R)- NH-CH($CH_2C_6H_5$)-CH_2-NH]}

(i) Cyclo{-Suc-Trp-Tyr-[(R)-NH-CH($CH_2C_6H_5$)-CH_2-NH]}

(j) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH($CH_2C_6H_3$-3,4-diCl)-CH_2-NH]}

(k) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH($CH_2C_6H_4$-4-OH)-CH_2-NH]}

(l) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-CH_2-C_6H_5)-CH_2-NH]}

(m) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-2-napthyl)-CH_2-NH]}

(n) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-indol-3-yl)-CH_2-NH]}

(o) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-5-F-indol-3-yl)-CH_2-NH]}

(p) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_4-3-F)-CH_2-NH]}

(q) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_3-3,4-diF-CH_2-NH]-}

(r) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_4-4-CF_3-CH_2-NH]-}

(s) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH_2-CH($CH_2C_6H_5$)-NH]}

(t) Cyclo{-Suc-Trp-Phe-[(S)-NH- CH_2-CH($CH_2C_6H_5$)-NH]}

(u) Cyclo{-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-(CH_2)$_3$CO-}

(v) Cyclo{-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-N(CH_3)]-(CH_2)$_3$CO-}

(w) Cyclo{-Suc[1(S)-NH_2]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

(x) Cyclo{-Suc[1(R)-NH_2]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

(y) Cyclo{-Suc[2(S)-NH_2]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

(z) Cyclo{-Suc[2(R)-NH_2]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

(aa) Cyclo{-Suc[1(S)-NH(CH_3)]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

(ab) Cyclo{-Suc[1-COO(CH_2-C_6H_4-4-NO_2)]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

(ac) Cyclo{-Suc(1-COOH)-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]}
[Cyclo{-Suc(1-COOH)-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]}]

(ad) Cyclo{-Suc(1-OH)-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]}

(ae) Cyclo{-Suc(2-COOH)-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]}

(af) Cyclo{-Suc(2-OH)-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]}

(ag) Cyclo{-Suc[1(S)-(2H-tetrazolyl-5-ylmethyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}trifluoro-acetic acid

(ah) Cyclo{-Suc[1(S)-(morpholin-4-yl)]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-} trifluoroacetic acid

(ai) Cyclo{-Suc[1(S)-N(CH_3)$_2$]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-} trifluoroacetic acid

(aj) Cyclo{-Suc[1(S)-(piperidin-4-yl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}trifluoroacetic acid

(ak) Cyclo{-Suc[1(S)-(N(CH_2CH_2OH)$_2$)]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]}trifluoroacetic acid

(al) Cyclo{-Suc[1(S)-(N($CH_2CH(OH)CH_2OH$)]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-} trifluoroacetic acid

(am) Cyclo{-Suc[1(S)-(3-carboxypropanoyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}.

(an) Cyclo{-Suc[1(S)-[3-N'-ß-D-glucopiranos-1-yl)-carboxamidopropanoyl]amino]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

(ao) Cyclo{-Suc[1(S)-[(carboxymethyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-} trifluoroacetic acid

(ap) Cyclo{-Suc[1(S)-[N'-ß-D-glucopiranos-1-yl)-carboxyamideomethyl]amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-} trifluoroacetic acid

(aq) Cyclo{-Suc[1(S)-(chinyl)amine]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}

(ar) Cyclo{-Suc[1(S)-(4-aminobutanoyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2- NH]-} trifluoroacetic acid

(as) Cyclo{-Suc[1(S)-[1,4')bipiperidin-1-yl]acetamido]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-} trifluoroacetic acid

(at) Cyclo{-Suc[1-N-(ß-D-glucopiranos-1-yl)-carboxyamido]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}; and

C2 date

(au) Cyclo{-Suc[1(S)-[N'-(2-N-acetyl-ß-D-glucopiranos-1-yl)-carboxyamido]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}.

C3

5. (Amended twice) A composition comprising a compound of general formula (I) according to Claim 1 in combination with a suitable carrier or excipient.

C4

9. (Amended twice) A composition according to claim 7, adapted for use as an anxiolytic.

12. (Amended twice) A method of antagonizing an NK-2 receptor in a mammal afflicted with asthma comprising contacting an NK-2 receptor in said mammal with a compound according to Claim 1 for a time and under conditions effective to antagonize said NK-2.

C5

13. (Amended twice) A method of antagonizing an NK-2 receptor in a mammal afflicted with an anxiety disorder comprising contacting an NK-2 receptor with a compound according to Claim 1 for a time and under conditions effective to antagonize said NK-2 receptor.

C6

14. (Amended twice) A method for the treatment of the bronchospastic and inflammatory component of asthma, coughing, pulmonary irritation, intestinal spasms, spasms of the biliary tract, local spasms of the bladder and if the ureter during cystitis, and kidney infections and colics, in which quantities of between 0.02 and 10 mg/kg of body weight of active principle consisting of a compound of formula (l), according to Claim 1, are administered to the patient for a time and under conditions effective to antagonize an NK-2 receptor.

Kindly cancel Claims 2 and 10

REMARKS

In the Office Action, Claims 1-3 and 5-18 were rejected under 35 U.S.C.§1121, first paragraph , as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, was in possession of the claimed invention.

Reconsideration is requested.

By this Amendment, the expression that was the basis of this ground of rejection has been deleted . Since the basis for the rejection has been removed, it is requested that this rejection be withdrawn.

Claims 8-9 and 14 were rejected under 35 U.S.C.§112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Reconsideration is requested.

The Examiner has stated that there is no evidence that the claimed compounds are effective to treat various diseases. The present rejection has been made under the provisions of 35 U.S.C.§112, first paragraph, which states that the specification must teach how to make and use an invention. In the present specification, the inhibition of NK-2 receptors as well as the specific conditions which may be treated have been disclosed. In addition, the dose at which such an effect is achieved has also been disclosed .See the specification at page 8, lines 4-5 and page 7, lines 13-26. This information enables the practice of the invention without undue experimentation. MPEP § 2164.01 points out experimentation may be complex without being "undue" provided that the art routinely engages in complex experimentation. The Examiner is asked to take note that the information which the Examiner states is necessary to enable one to "make and use" the claimed invention is of the type that is routinely developed in the course of developing any new chemical entity having pharmaceutical activity.

The therapeutic utility statement is not to be confused with the requirements of the FDA which the Examiner appears to be referencing in noting that there is no evidence that the compounds are effective to treat various diseases. No such evidence is required in order to support a patent. The disclosure of the use of a new chemical compound and a dose at which the compound is to be used provides one who is skilled

in the art with the information to go to the next step in pharmaceutical development by using non-inventive and ordinary skill to carry out experiments to optimize the use of a particular compound. The Examiner invited to note MPEP2107 where Examiner's are instructed not to impose a 35 U.S.C.§112, first paragraph rejection grounded on a lack of utility.

The Examiner has cited four references in support of the rejection under 35 U.S.C.§112, first paragraph. None of the cited references address the level of skill and the standard techniques that are used by pharmacologists in the drug industry who, as a part of their routine activities, receive a sample of a new chemical substance from a chemist with a suggestion of a use for the chemical substance and thereafter carry out a series of routine experiments to verify the activity of the drug for the suggested use and to establish a dose for the particular drug. In the present specification, the disclosure of specific conditions and a dose provides a starting point for carrying out additional experimentation to complete the development of a clinically useful drug.

The four cited references are concerned with biological effects of different drugs that are used for different conditions. The conditions include melanoma, diabetes and opioid activity. These conditions are remote from the claimed utility for the new compounds defined by the claims of the present application.

The content and scope of the disclosure of the present application is quite similar to the content and scope of thousands of issued U.S. patents that are directed to pharmaceutical compounds.

Attached hereto are copies of Holzer et al, Evangelista et al. and Rogers which are publications which relate to the state of the art as regarding the relation of tachykinin receptor antagonists and various physiological actions. The Examiner is asked to note that the attached Duncan F. Rogers publication , Expert Opin, Ther. Patent (11) 7 1097-1121 refers to the relationship of tachykinin and NK-2 activity with regard to various pharmaceutically active compounds. For these reasons, it is requested that this ground of rejection be withdrawn.

Claims 1-3 and 5-15 were rejected under 35 U.S.C. § 112, second paragraph,. as being indefinite for failing to particularly point out and distinctly claim the subject matter that the applicant regards as to invention.

Reconsideration is requested.

The term "anxiolytics" in Claim 9 has been rewritten in the singular. This use is enabled by the disclosure at pages 7 and 8. Claims 2 and 10 have been canceled and the portions of claim 2 that have been inserted into claim 1 have been revised to avoid each of the informalities noted by the Examiner.

Claims1-2 were rejected under 35 U.S.C. §102(b) as being anticipated by Rothe, M. (*Pept Proc Eur Pept Symp* 14th, 71-8, 1976). Specifically, the Examiner stated that Claim 1 includes the compound cyclo-Phe-Phe-Val-Val. As amended, claim 1 points out that the definition of L no longer allows R_4 to be H or alkyl. This Amendment avoids any possibility that the Rothe, M. compounds could read on the claimed compounds. For this reason, it is requested that this ground of rejection be withdrawn.

Claims 1-2 , 5-9 and 15 were rejected under 35 U.S.C.§103(a) as being unpatentable over Kitakabake.

Reconsideration is requested.

The four amino acids in the compound discovered by Kitakabake do not render the claimed compounds structurally obvious in the sense of 35 U.S.C. §103(a). The ordering of the amino acids within the present invention leads to vastly different interactions then would the ordering that is taught by the prior art. Furthermore valine is excluded as a R1 and R2 substituent of the Markush group of the existing claims. .

The compounds of the present invention are distinctly different from the Kitakabake compounds and there is no suggestion in Kitakabake to prepare modified compounds.

In order to demonstrate that there is a prima facie case of obviousness, the structure of the compounds must be so close that by inspection that one would be motivated to modify the prior art compounds because there is no suggestion in the cited prior art to carry out any modification. There is no reason to substitute the leucine or isoleucine into the Kitakabake peptides other than the applicants specification. This is not the typical case of structural obviousness where a carbon chain is lengthened or a halogen is substituted for another halogen. A completely different amino acid is involved in the claimed compounds and the use of these amino acids is not taught by the cited prior art patent.In this situation, a secondary reference must teach or direct the substitution of a different amino acid in order to support a rejection for obviousness. For these reasons, it is requested that the rejections to the present claims be withdrawn.

Based on the amendments, applicant respectfully submits that all claims are now allowable over the prior art and that the present application is in proper form for allowance.

Favorable consideration and early allowance is respectfully requested and earnestly solicited.

Respectfully submitted,

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